REMARKS

Claims 45-54 and 56-72 are pending in this application. Claims 45-54 and 56-72 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld (U.S. Patent No. 4,016,252; hereinafter "Relyveld") in combination with Poser et al. (U.S. Patent No. 5,968,253; hereinafter "Poser"). Claims 49-54, 56-57, and 64-71 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld in combination with Poser and Classen (U.S. Patent No. 5,723,283; hereinafter "Classen"). Claims 47-48 and 62-63 are rejected under 35 U.S.C. § 103(a) for obviousness over the combination of Relyveld, Poser, Classen, and Lee et al. (U.S. Patent No. 6,541,037; hereinafter "Lee"). Finally, claims 45-54 and 56-72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,214,368 (hereinafter "the '368 patent"), claims 1-7 of U.S. Patent No. 6,117,456 (hereinafter "the '456 patent"), and claims 1-12 of U.S. Patent No. 5,683,461 (hereinafter "the '461 patent"). By this reply, Applicants cancel claims 47-48 and 62-63 and address each of the Examiner's rejections.

Rejections under 35 U.S.C. § 103

Relyveld in Combination with Poser

Claims 45-54 and 56-72 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld in combination with Poser. By the accompanying Combined Declaration under 37 C.F.R. § 1.131 and § 1.132, Poser has been removed as a prior art reference.[1]

[1] By submitting the § 131 Declaration, Applicants are not conceding that the subject matter of present claims 45-54 and 56-72 is obvious over the combination of Relyveld and Poser.

Applicants direct the Examiner to *In re Scheiber* (587 F.2d 59, 199 U.S.P.Q. 782 (C.C.P.A. 1978)), which states that "Rule 131...provides an applicant a mechanism for overcoming specific prior art references predating his effective filing date. The applicant need show priority with respect to only so much of the claimed invention as the references disclose ... or only so much as to render the claimed invention obvious..." (citing *In re Stempel*, 241 F.2d 755, 113 U.S.P.Q. 77 (C.C.P.A. 1957)). The Combined Declaration under 37 C.F.R. § 1.131 and § 1.132 states that at least as much of the subject matter disclosed by Poser was reduced to practice by Applicants prior to July 31, 1998 (the earliest priority date of Poser). As evidence, Applicants provide a copy of PCT/US97/18528 (Exhibit A), which was filed on October 16, 1997, and which teaches the preparation of a vaccine delivery composition that includes a calcium phosphate and an antigen (see, e.g., page 8, lines 2-5, and page 35, line 11, through page 36, line 4, of PCT/US97/18528; a copy of which is enclosed). The Declaration also attests that D. Duke Lee and Maria Aiolova, who are named as the inventors of the present application and as co-inventors on PCT/US97/18528, are the only inventors of the relevant subject matter described in PCT/US97/18528; the third inventor named on PCT/US97/18528, Christian Rey, did not contribute to that subject matter.[2] Because the attached Declaration under 37 C.F.R. § 1.131 clearly shows Applicants' possession of "so much of the claimed invention" as Poser discloses (*In re Scheiber, supra*), Poser can now be withdrawn as prior art to the present application.

In the absence of Poser, the rejection of claims 45-54 and 56-72 for obviousness in view

[2] Applicants regretfully note that Inventor D. Duke Lee is deceased. Accordingly the Declaration is only signed by the co-inventor, Maria Aiolova; a copy of his Certificate of Death is enclosed.

of Relyveld alone cannot be sustained because Relyveld, which discloses an aqueous gel of calcium phosphate for preparing adsorbed vaccines (see, e.g., the abstract), fails to teach or suggest a calcium phosphate-based vaccine formulation having a solids content of greater than or equal to 40 wt%. Moreover, by disclosing an aqueous gel formulation, Relyveld directly teaches away from the composition recited in present claims 45-54 and 56-72, which further rebuts the conclusion that Relyveld, in combination with any reference, would lead the skilled artisan to Applicants' claimed immunological vaccine delivery composition (see, e.g., M.P.E.P. § 2144.05(III)). Accordingly, Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of claims 45-54 and 56-72 over Relyveld in combination with Poser be withdrawn.

Relyveld in Combination with Poser and Classen

Claims 49-54, 56-57, and 64-71 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld in combination with Poser and Classen. As is discussed above, Poser is not prior art to the present application. In the absence of Poser, the rejection cannot be sustained because Relyveld and Classen, either singly or in combination, fail to teach or suggest each and every limitation of present claims 49-54 56-57, and 64-71. Relyveld is discussed *supra*. Classen discloses a traditional vaccine formulation that contains, *inter alia*, an immunogen (see, e.g., col. 15, line 30, through col. 20, line 34) and an adjuvant (e.g., calcium phosphate salts; col. 20, lines 35-50), which are diluted in phosphate buffered saline (PBS; see, e.g., col. 35, lines 23-38). Classen, like Relyveld, fails to teach or suggest the administration of an immunogen using a composition having a solids content of greater than or equal to 40 wt% and that is hardenable. Thus, Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of claims 49-54, 56-

57, and 64-71 over Relyveld in combination with Poser and Classen be withdrawn.

Relyveld in Combination with Poser, Classen, and Lee

Claims 47-48 and 62-63 are rejected under 35 U.S.C. § 103(a) for obviousness over the combination of Relyveld, Poser, Classen, and Lee. Applicants have cancelled claims 47-48 and 62-63. Accordingly, this rejection can now be withdrawn.

Obviousness-Type Double Patenting Rejections

The Examiner rejects claims 45-54 and 56-72 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of the '368 patent, claims 1-7 of the '456 patent, and claims 1-12 of the '461 patent. Applicants have cancelled claims 47-48 and 62-63. Therefore, Applicants respectfully traverse these rejections, each of which is discussed below, as they apply to pending claims 45-46, 49-54, 56-61, and 64-72.

The Requirements for Obviousness-type Double Patenting

M.P.E.P. § 804(II)(B)(1) states that "the first question to be asked is - does any claim in the application define an invention that is merely an obvious variation of an invention claimed in a patent? If the answer is yes, then an 'obviousness-type' nonstatutory double patenting rejection may be appropriate." M.P.E.P. § 804(II)(B)(1) also states that:

> A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the non-obviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

The question of obviousness, in cases of double patenting, is addressed using the criteria

established under 35 U.S.C. § 103. A finding of obviousness under 35 U.S.C. § 103 is only affirmed if all of the claim limitations are taught or suggested in the cited patent or patents on which the rejection is based (*In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)). The patent specification cannot be used as prior art and obviousness must be determined based solely on the claims of the '368 patent (see *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970)). Furthermore, in *Vogel*, the Court of Customs and Patent Appeals, the predecessor to the Federal Circuit, held that if the rejected claim defines more than an obvious variation, it is patentably distinct (*Id* at 442). In *Vogel*, the C.C.P.A. described an "obvious variation" as an aspect of the claimed subject matter that can be modified based on knowledge in the prior art (i.e., the permeability range of the packaging material; *Id* at 442).

Finally, obviousness can only be established by modifying the teachings of the prior art (here the claims of the '368 patent) where there is some teaching, suggestion, or motivation to do so found *in the reference* (see, e.g., *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000)).

Rejection of Claims 45-46, 49-54, 56-61, and 64-72 over Claims 1-11 of the '368 Patent

As is discussed above, Applicants' pending claims 45-46, 49-54, 56-61, and 64-72 are directed to an immunological vaccine delivery composition (claims 45-46, 49-54, and 56-58) and its use (claims 59-61 and 64-72), in which the composition is formulated as a hardenable, injectable paste having a solids content of greater than or equal to 40 wt% and includes a calcium phosphate and an immunogen which elicts a host immune response that protects a host against a pathogen. Claim 1 of the '368 patent, from which claims 2-11 depend, is directed to a formable

paste and reads as follows:

> 1. A formable paste, suitable for use as a bone substitution material, comprising:
>
> a powder comprising a first calcium phosphate material having at least 90% amorphous character and an acidic second calcium phosphate material, the powder having a calcium to phosphorous molar ratio in the range of about 1.2 to 1.68; and
>
> a fluid in an amount to provide a formable or injectable consistency, said paste remaining injectable or formable for a time greater than about 60 minutes at about 22°C and hardenable within about 30 minutes at about 37°C, said paste suitable for use as a bone substitute material.

Claims 2-11 of the '368 patent, which depend from claim 1, are directed to embodiments of the paste, such as its formation and hardening characteristics (claims 2 and 5), its X-ray diffraction characteristics (claim 3 and 4), the calcium and phosphate sources of the powder components (claims 6, 8, 9, 10, and 11), and the source of the fluid (claim 7). Claims 1-11 of the '368 patent do not recite the inclusion of any supplemental materials, such as an *immunogen*, as is recited in independent claims 1, 59, and 60, and claims dependent therefrom. Thus, the vaccine delivery composition of claims 45-46, 49-54, 56-61, and 64-72 is distinct from the formable paste recited in claims 1-11 of the '368 patent.

Claims 45-46, 49-54, 56-61, and 64-72 also do not define a composition that is merely an obvious variation of the formable paste recited in claims 1-11 of the '368 patent. The vaccine delivery composition recited in present claims 45-46, 49-54, 56-61, and 64-72, which includes an immunogen that elicits a host immune response that protects a host against a pathogen, can certainly not be considered an obvious variant when claims 1-11 of the '368 patent do not recite or suggest a formable paste that includes any supplemental materials, much less an immunogen.

Therefore, claims 45-46, 49-54, 56-61, and 64-72, which are directed to a vaccine delivery composition, do not read on and do not define merely an obvious variation of the bone substitution material of claims 1-11 of the '368 patent. Accordingly, Applicants submit that the vaccine delivery composition and methods of its use, recited in claims 45-46, 49-54, 56-61, and 64-72, are clearly distinct from, and non-obvious in view of, the formable paste recited in claims 1-11 of the '368 patent.

Furthermore, the Examiner has not met the burden of showing that the formable paste recited in claims 1-11 of the '368 patent constitutes an obvious variation of the presently claimed vaccine delivery composition. One skilled in the art would not be directed, based solely on claims 1-11 of the '368 patent, to prepare the presently claimed vaccine delivery composition, due to the lack of any teaching or suggestion to do so (see *In re Kotzab*, *supra*). Therefore, for all of the reasons provided above, Applicants respectfully request that the rejection of claims 45-46, 49-54, 56-61, and 64-72 for obviousness-type double patenting over claims 1-11 of the '368 patent be withdrawn.

Rejection of Claims 45-46, 49-54, 56-61, and 64-72 over Claims 1-7 of the '456 Patent and over Claims 1-12 of the '461 Patent

Claims 45-46, 49-54, 56-61, and 64-72 also stand rejected for obviousness-type double patenting over claims 1-7 of the '456 patent and over claims 1-12 of the '461 patent. The Examiner states:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to compositions comprising amorphous calcium phosphate for in vivo use. Further both sets of claims only vary in amounts of calcium phosphate

> concentrations withing the claimed compositions. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to optimize such amounts by routine experimentation. Accordingly, the scope of the claims overlap and thus are obvious variants of each other. (Office Action dated September 22, 2004, p. 4.)

Applicants also traverse the rejection of claims 45-46, 49-54, 56-61, and 64-72 for obviousness-type double patenting over claims 1-7 of the '456 patent and over claims 1-12 of the '461 patent because these claims do not recite or suggest the same composition as, or an obvious variant of, the composition recited in claims 45-46, 49-54, 56-61, and 64-72 of the present application.

Independent claim 1 of the '456 patent is directed to a reactive amorphous calcium phosphate material and reads as follows:

> 1. A reactive amorphous calcium phosphate material having at least 90% percent amorphous character and characterized in that, when prepared 1:1 as a mixture with dicalcium diphosphate in water, the mixture remains injectable and formable for a time greater than about 60 minutes at about 25°C and hardens at about 37°C within about 10 to about 60 minutes.

Claims 2-7 of the '456 patent, which depend from claim 1, are directed to embodiments of the reactive amorphous calcium phosphate, such as its surface area (claims 2 and 3), its pore size (claim 4), its hardening time (claim 5), its calcium to phosphate ratio (claim 6), and the source of its reactivity (claim 7). Claims 1-7 of the '456 patent do not recite the inclusion of an immunogen, as is recited in independent claims 1, 59, and 60, and claims dependent therefrom, nor would one skilled in the art be directed, based solely on claims 1-7 of the '456 patent, to prepare the presently claimed vaccine delivery composition.

Independent claims 1 and 9 of the '461 patent are directed to an injectable paste and its use, respectively. Claims 1 and 9 are reproduced below.

> 1. An injectable paste comprising:

a decarbonated amorphous calcium phosphate prepared by removing by thermal decomposition at least a portion of a carbonate component from a carbonated amorphous calcium phosphate;

a second calcium phosphate, the second calcium phosphate and amorphous calcium phosphate present in a proportion to provide a Ca/P ratio characteristic of an apatitic calcium phosphate; and

an amount of aqueous medium sufficient to provide a paste of a desired consistency,

characterized in that when in a moist tissue environment and upon reaching body temperature (37°C), the paste hardens into a poorly crystalline hydroxyapatite without exothermic behavior.

9. A method of promoting bone growth, comprising:

identifying a site requiring bone growth;

applying to the site a paste comprising:

a decarbonated amorphous calcium phosphate prepared by removing by thermal decomposition at least a portion of the carbonate component from a carbonated amorphous calcium phosphate;

a second calcium phosphate, the second calcium phosphate and amorphous calcium phosphate present in a proportion to provide a Ca/P ratio characteristic of an apatitic calcium phosphate; and

an amount of aqueous medium sufficient to provide a desired consistency; and allowing the paste to harden without exothermic behavior, whereby a poorly crystalline hydroxyapatite is formed.

Claims 2-8, which depend from claim 1, and claims 10-12, which depend from claim 9, are directed to embodiments of the injectable paste, such as its injection characteristics (claims 2 and 11), its thermal decomposition characteristics (claims 3 and 12), the source and characteristics of the second calcium phosphate (claims 4 and 5), the type of supplemental materials (claims 6, 7, and 10), and the characteristics of the aqueous medium (claim 8). Claims 1-12 of the '461 patent do not recite the inclusion of an immunogen, as is recited in independent claims 1, 59, and 60,

and claims dependent therefrom, nor would one skilled in the art be directed, based solely on claims 1-12 of the '461 patent, to prepare the presently claimed vaccine delivery composition.

A review of the relevant claims of the '456 and '461 patents which, for obviousness-type double patenting determinations, is the only portion of the patent specification that may be reviewed,[3] does not reveal any teaching or suggestion to include an immunogen in the reactive amorphous calcium phosphate material or the injectable paste, respectively. Therefore, the vaccine delivery composition of present claims 45-46, 49-54, 56-61, and 64-72 is not the same composition as, and is distinct from, the composition recited in claims 1-7 of the '456 patent or claims 1-12 of the '461 patent because neither the reactive amorphous calcium phosphate material of claims 1-7 of the '456 patent or the injectable paste of claims 1-12 of the '461 patent includes an immunogen, as is required by claims 45-46, 49-54, 56-61, and 64-72 of the present application.

The vaccine delivery composition recited in claims 45-46, 49-54, 56-61, and 64-72 is also more than an obvious variation of the reactive amorphous calcium phosphate material recited in claims 1-7 of the '456 patent and the injectable paste recited in claims 1-12 of the '461 patent. Claims 1-7 of the '456 patent and claims 1-12 of the '461 patent do not recite or suggest that the reactive amorphous calcium phosphate material or the injectable paste, respectively, includes an immunogen. Although claims 6, 7, and 10 of the '461 patent specify that the injectable paste can include a bone regenerative protein or an antibiotic, these components are not disclosed as being immunogens, and, in fact, are not included in the '456 and '461 compositions for use as an

[3] The portions of the patent specification that disclose the subject matter recited in the relevant claims may also be reviewed, but only to the extent that the specification acts as a dictionary to define terms recited in the claims that require clarification. *See In re Vogel, supra.*

immunogen. Moreover, one skilled in the art would not understand them to be immunogens. Therefore, claims 45-46, 49-54, 56-61, and 64-72, which are directed to a vaccine delivery composition, do not read on and do not define merely an obvious variation of the reactive amorphous calcium phosphate material of claims 1-7 of the '456 patent or the injectable paste of claims 1-12 of the '461 patent. Accordingly, Applicants submit that the vaccine delivery composition and methods of its use, recited in claims 45-46, 49-54, 56-61, and 64-72, are clearly distinct from, and non-obvious in view of, the reactive amorphous calcium phosphate material recited in claims 1-7 of the '456 patent and the injectable paste recited in claims 1-12 of the '461 patent.

Applicants again submit that the Examiner has not met the burden of showing that either the reactive amorphous calcium phosphate material recited in claims 1-7 of the '456 patent or the injectable paste recited in claims 1-12 of the '461 patent constitutes an obvious variation of the presently claimed vaccine delivery composition. One skilled in the art would not be directed, based solely on claims 1-7 of the '456 patent or claims 1-12 of the '461 patent, to prepare the presently claimed vaccine delivery composition, due to the lack of any teaching or suggestion in the claims of these patents to do so (see *In re Kotzab*, *supra*). Therefore, for all of the reasons provided above, Applicants respectfully request that the rejection of claims 45-46, 49-54, 56-61, and 64-72 for obviousness-type double patenting over claims 1-7 of the '456 patent and over claims 1-12 of the '461 patent be withdrawn.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the claims are in condition for allowance, and such action is respectfully requested.

If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Todd Armstrong, Ph.D.
Reg. No. 54,590

Date: 15 February 2006

for Paul T. Clark
Reg. No. 30,162

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

VITAL RECORDS CERTIFICATE

Y407530 CHANGES APPROVED BY COMMR OF HEALTH SEP 16 2004

DATE FILED
NEW YORK CITY DEPARTMENT OF HEALTH AND MENTAL HYGIENE
7/21/2004 4:01:47 PM

THE CITY OF NEW YORK – DEPARTMENT OF HEALTH AND MENTAL HYGIENE

CERTIFICATE OF DEATH

Certificate No. 156-04-031588

1. DECEDENT'S LEGAL NAME DUKE (First Name) — (Middle Name) — LEE (Last Name)

MEDICAL CERTIFICATE OF DEATH (To be filled in by the Physician)

Place Of Death
2a. New York City
2b. Borough: MANHATTAN
2c. Type of Place: 1 [X] Hospital Inpatient; 2 [ ] Emergency Dept./Outpatient; 3 [ ] Dead on Arrival; 4 [ ] Nursing Home/Long Term Care Facility; 5 [ ] Hospice Facility; 6 [ ] Decedent's Residence; 7 [ ] Other Specify
2d. Name of hospital or other facility (if not facility, street address): NEW YORK PRESBYTERIAN HOSPITAL

Date and Time of Death	3a. (Month)	(Day)	(Year-yyyy)	3b. Time	4. Sex	5. Date last attended by a Physician mm	dd	yyyy
	JULY	19	2004	7:25 [ ] AM [X] PM.	MALE	07	19	2004

6. Certifier: I certify that death occurred at the time, date and place indicated and that to the best of my knowledge traumatic injury or poisoning DID NOT play any part in causing death, and that death did not occur in any unusual manner and was due entirely to NATURAL CAUSES. See instructions on reverse of certificate.

Name of Physician (Type or Print): RACHEL KUPERMAN
Signature: [signature] D.O. / M.D.
Address: 622 WEST 168 STREET NEW YORK
License No. 230533 Date 07/19/2004

PERSONAL PARTICULARS (To be filled in by Funeral Director or, in case of City Burial, by Physician)

7a. Usual Residence State	7b. County	7c. City or Town	7d. Street and Number	Apt. No.	ZIP Code	7e. Inside City Limits?
MA		Cambridge	130 Mt. Auburn St.	108	02138	[X] Yes [ ] No

8. Date of Birth (Month)	(Day)	(Year-yyyy)	9. Age at last birthday (years)	Under 1 Year: Months	Days	Under 1 Day: Hours	Minutes	10. Social Security No.
August	8,	1957	46					072-48-6258

11a. Usual Occupation (Type of work done during most of working life. Do not use "retired")	11b. Kind of business or industry	12. Aliases or AKAs
Employee	President Cambridge Med	Dosuk Duke Lee

13. Birthplace (City & State or Foreign Country): Korea MISSOURI, U.S.A

14. Education (Check the box that best describes the highest degree or level of school completed at the time of death): 1 [ ] 8th grade or less; 2 [ ] 9th – 12th grade; no diploma; 3 [X] High school graduate or GED; 4 [ ] Some college credit, but no degree; 5 [ ] Associate degree (e.g., AA, AS); 6 [X] Bachelor's degree (e.g., BA, AB, BS); 7 [ ] Master's degree (e.g., MA, MS, MEng, MEd, MSW, MBA); 8 [ ] Doctorate (e.g., PhD, EdD); 9 [ ] Professional degree (e.g., MD, DDS, DVM, LLB, JD)

15. Ever in U.S. Armed Forces?	16. Marital Status at Time of Death	17. Surviving Spouse's Name (If wife, name prior to first marriage) (First, Middle, Last)
1 [ ] Yes 2 [X] No	1 [X] Married 3 [ ] Married, but separated 5 [ ] Widowed 2 [ ] Divorced 4 [ ] Never married 6 [ ] Unknown	Youngmi M. [illegible]SUN

18. Father's Name (First, Middle, Last)	19. Mother's Maiden Name (Prior to first marriage) (First, Middle, Last)
Jean Myung Lee	Soo Won Lee

20a. Informant's Name	20b. Relationship to Decedent	20c. Address (Street and Number, Apt. No., City & State, ZIP Code)
Youngmi M. Lee	wife	49 Palmer Ave., Scarsdale, NY

21a. Method of Disposition: 1 [ ] Burial 2 [X] Cremation 3 [ ] Entombment 4 [ ] City Cemetery 5 [ ] Other Specify

21b. Place of Disposition (Name of cemetery, crematory, other place): Forest Hills Crematory

21c. Location of Disposition (City & State or Foreign Country): Boston, Massachusetts

21d. Date of Disposition: mm dd yyyy: 07-22-2004

22a. Funeral Establishment: Central Funeral Home

22b. Address (Street and Number, City & State, ZIP Code): 136-25 41 Ave., Flushing, NY

VR 15 (Rev. 01/03)

BEST AVAILABLE COPY

This is to certify that the foregoing is a true copy of a record on file in the Department of Health and Mental Hygiene. The Department of Health and Mental Hygiene does not certify to the truth of the statements made thereon, as no inquiry as to the facts has been provided by law.

Steven P. Schwartz, Ph.D., City Registrar

Do not accept this transcript unless it bears the security features listed on the back. Reproduction or alteration of this transcript is prohibited by §3.21 of the New York City Health Code if the purpose is the evasion or violation of any provision of the Health Code or any other law.

DATE ISSUED: SEPTEMBER 28, 2004 DOCUMENT No. P335855

The City of New York